DRAFT: FDA Questions for the Circulatory System Devices Advisory Panel
May 6, 2014

P110024
ResQCPR™ System

1. Study Design

Please comment on the following study design issues. How significant were they and what impact, if any, do you believe they have on interpretation of final study safety and effectiveness results?

Q1a. The relative contribution of active compression/decompression CPR, and the impedance-threshold device alone could not be fully determined (as the ITD arm of the study was dropped early in the course of the study), and results from ROC PRIMED do not support effectiveness of the ITD alone for improving survival with favorable neurologic function

Q1b. The DSMB protocol did not prospectively lay out a clear method for possible sample size increase with preservation of alpha.

Q1c. DSMB records which effectively unblinded, and allowed for complete unblinding, of the study were available to the sponsor. Note that the sponsor maintains it was never completely or inappropriately unblinded throughout the study.

Q1d. Some endpoint determinations (modified Rankin Score) were formulated in the absence of structured, in-person patient interviews, often at times distant from the date of hospital discharge.

Q1e. The primary analysis excluded patients with cardiac arrests of "non-cardiac" etiology, such as drug overdose or metabolic abnormalities.

Q1f. Although the gender sub-group analysis was not statistically powered, the observed treatment effect in women was 18% less than the treatment effect in men.

Q1g. Emergency medical service rescuers were not blinded to the CPR method; however, assessors of the primary outcome and neurological tests were masked to intervention status.

2. Evaluation of Safety

The primary safety endpoint of the ResQCPR™ Trial was non-inferior to s-CPR (Table 15 from Executive Summary below). Individual complication rates are also noted and, pulmonary edema

(11.2% treatment arm vs. 7.6% control arm) was higher in the ACD-ITD arm (Pulmonary Edema information extracted from Table 10.1 from P110024 is provided below).

Table 15: Final outcome for the secondary safety endpoint: major adverse event (mITT) (By FDA)

	S-CPR (N=813)	**ACD-ITD (N=842)**	**Difference of s-CPR from ACD-ITD [ACD-ITD] – [S-CPR] (95.6% C.I)**
Pivotal	93.8% (763/813)	92.9% (782/842)	-0.98% (-3.5%, 1.5%)

Note: The upper bound of 95.6% CI should be compared with the non-inferiority margin of 5%

Secondary Safety Endpoint Analysis: Pulmonary Edema through hospital discharge, mITT

Event	**S-CPR (N=813)**	**ACD-ITD (N=842)**	**P-Value**
Pulmonary Edema	62 (7.6%)	94 (11.2%)	0.015

Q2a. Please comment on the overall safety results and specifically on the difference in pulmonary edema rates. In doing so please indicate whether any of the study design issues discussed in question 1 significantly affect your conclusions regarding device safety.

3. Evaluation of Effectiveness

Based on the sponsor's dataset, the primary endpoint (survival with good neurologic outcome) was met in the mITT population. The primary endpoint and the hypothesis-driven secondary effectiveness endpoints were not met in the ITT population. Additional post-hoc analyses were performed in an attempt to understand the effect of missing and/or changed data on the primary analysis, as well as the sensitivity of these results to the data. Most of these analyses did not meet the primary endpoint($p > 0.049$)

Q3a. Please comment on your overall assessment of device effectiveness taking into account both the primary endpoint effectiveness result and the supporting adjunctiveprimary analyses results. In doing so please indicate whether any of the study design issues discussed in question 1 significantly affect your conclusions regarding device effectiveness.

Q3b. Please discuss the significance of the pre-specified secondary Neurological endpoint results. Do the neurological results rule out any significant increase in the percentage of patients in the ACD-ITD arm who may suffer significant acute or chronic neurological impairment compared to the S-CPR arm?

4. Benefit Risk Profile

Q4a. Given the device's safety profile, the totality of the evidence regarding effectiveness, and the clinical significance of these results, please comment on the benefit risk profile of this device.

5. Device Labeling

One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify the product's potential adverse events, and explain how the product should be used to maximize benefits and minimize adverse effects.

Q5a. The ResQTrial was carried out in subjects 18 years of age or older. Please comment on whether the Indications for Use statement should specifically indicate use in adults only.

Q5b. The principal results from the ResQTrial derive from a very specific subset of cardiac arrest patients, i.e., those patients definitively lacking certain comorbidities and/or characteristics that could precipitate or facilitate the occurrence of cardiac arrest. Since FDA feels it is neither reasonable nor practical to expect rescuers to elucidate the arrest etiology before using the device, please discuss any labeling considerations that should/should not be placed on the device based on the data presented today on the specific patient population studied in the ResQTrial.

6. Post-Approval Study (PAS)

Q6a. Please comment as to whether or not you believe a post-approval study is practical and beneficial for further evaluation of the ResQCPR System, should the System be approved as intended.